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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/600,129	06/19/2003	Sarah S. Bacus	02-434-A	9778

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EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/600,129	BACUS ET AL.	
	Examiner	Art Unit	
	ANNE L. HOLLERAN	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *1-28 and 35-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/20/2008 has been entered.

Claims 1-38 are pending. Claims 1-28 and 35-38, drawn to non-elected inventions, are withdrawn from consideration. Claims 29-34 are pending and examined on the merits.

Claim Rejections Withdrawn:

Claim Rejections - 35 USC § 112-second paragraph

The rejection of claims 29-32 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the phrase "low level of expression" is withdrawn in view of the amendments to the claims.

Claim Rejections - 35 USC § 112-first paragraph

The rejection of claims 30, 32 and 34 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not set forth in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention is withdrawn upon further consideration. Specifically, in US 6,235,883, which is incorporated by reference in the instant specification, at column 20, lines 32-39, 8 anti-EGFR antibodies are described as having fully human IgG2 heavy chains with human kappa light chains, and further structural information with respect to the kappa light chains is provided in column 30, lines 4-30. Further, the variable regions of the 8 anti-EGFR antibodies are described at column 24, line 11 through to column 29, line 36.

Claim Rejections - 35 USC § 103

The rejection of claims 29, 31 and 33 under 35 U.S.C. 103(a) as being unpatentable over Herbst (Herbst, R.S. et al., Expert Opin. Biol. Ther., 1(4): 719-732, 2001) in view of Xia (Xia, W. et al. Clinical Cancer Res. 5: 4164-4174, 1999) is withdrawn in view of the amendment to the claims.

The rejection of claims 29-34 under 35 U.S.C. 103(a) as being unpatentable over Herbst (Herbst, R.S. et al., Expert Opin. Biol. Ther., 1(4): 719-732, 2001) in view of Xia (Xia, W. et al. Clinical Cancer Res. 5: 4164-4174, 1999) and further in view of Yang (Yang, X.-D. et al., Critical Reviews in Oncology/Hematology, 38: 17-23, 2001) is withdrawn in view of the amendment to the claims.

New Grounds of Rejection:

Claim Objections

Claim 29 is objected to for using the abbreviation "OD" with first spelling out the term in its entirety. Correction is required.

Claim Rejections - 35 USC § 112-second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30, 32 and 34 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 30, 32 and 34 are indefinite because it is not clear if "ABX-0303" refers to a single antibody species or to a genus of antibodies. Claims 30, 32 and 34 recite an antibody that is "ABX-0303". The specification refers to US Patent 6,235,883 for teaching the "ABX-0303". However, US Patent 6,235,883 describes 8 different antibodies and does not use the term "ABX-0303" as used in the instant claims, nor "ABX-EGF" referred to in the specification as a term associated with any one of the 8 different antibodies. It is unclear what the scope of the claims is, because using the term "ABX-0303" implies a single antibody species, whereas the teachings of US Patent 6,235,883 teaches 8 different anti-EGFR antibodies.

Claim Rejections - 35 USC § 112-first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating subjects having renal cancer comprising first selecting the patient population by detecting levels of HER3, where the cut-off for selection is an OD less than 9 as determined by quantitative immunohistochemistry, does not reasonably provide enablement for treating a subject with any type cancer comprising first selecting a patient population using the method recited in the claims and the cut-off for selection recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

The claims are drawn to methods of treating subjects with cancer comprising first assaying a cell or tissue sample from the subject to detect an expression level for HER3. The

intended use of this method step is to select for patients that will be treated with an anti-EGFR antibody. The claims recite that the cut-off of the optical density (OD) determined by quantitative immunohistochemistry is less than 9.

Esteva (Esteva, F. J. et al., Pathology Oncology Research, 7(3): 171-177, 2001) teaches that optical density measurements are arbitrary units used to indicate the amount of antigen on tissues (see page 173 1st to 2nd column, bridging paragraph). Esteva appears to use a method similar to that described in the instant specification, but found much lower cut-offs for determining high versus low levels of tumor markers (see Table 1, page 173) than what is recited in the specification. The specification confines its examples of using the level of Her3 expression as a factor in assessing possible responsiveness to an anti-EGFR antibody to the example of renal cancer tissues. There is no indication in the specification nor in the prior art that the results having using a cut-off of optical density of less than 9 would be appropriate for cancers other than renal cancer as exemplified in the specification. Therefore, the recitation in the claims that a cut-off optical density level of less than 9 appears for the measurement of Her3 levels appears to be specific to renal cancers and does not appear to be applicable to any and all cancers.

In view of the limited disclosure of the specification and the use of the specific optical density cut-off assessing responsiveness to an anti-EGFR antibody, the broad scope of the claims, which are drawn to methods of treatment of any and all cancers does not appear to be enabled by the specification. One of skill in the art would have to engage in undue further experimentation to determine if the optical density cut-off of 9 for the measurement of Her3 levels would be appropriate for identifying appropriate patients for treatment with an anti-EGFR

antibody, because there is no indication that the cut-off recited in the claims is appropriate for other cancers.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 29, 31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudziak (US 5,770,195; issued Jun. 23, 1998) in view of Esteva (Esteva, F. J. et al., Pathology Oncology Research, 7(3): 171-177, 2001).

The claimed methods comprise two active steps: that of assaying for the expression level of HER3 in cells from a cancer and the second step of treating the subject with an EGFR antibody if the HER3 expression levels detected have an OD less than 9 when determined by quantitative immunohistochemistry that the subject is treated.

Hudziak teaches and claims a method of treating cancer that expresses EGF receptor with an anti-EGFR antibody (see claims 14-33). Hudziak fails to teach a patient selection step of first measuring levels of Her3 in a sample from a patient.

Esteva teaches measuring levels of EGFR, Her-2, Her-3, Her-4, heregulin, P-p38 (phosphorylated p38), P-MAPK(phosphorylated MAPK) and P-Her-2 (phosphorylated Her-2). For Her-3, Esteva teaches that a median OD level of 0.85 is the cutpoint to discriminate between high and low levels. MAPK is a synonym for Erk (see Database PIR, Accession No. P28482 (MK01_Human, Georgetown University, Washington, DC, Version 95, 2/26/2008). Esteva teaches that tumors that express HER-3 and HER-4 exhibit cellular growth and drug resistance and that HER-3 and HER-4 have been shown to be receptors to other growth factors (such as EGF an EGFR growth factor, see reference #41 and page 176, first column). Esteva also teaches that identification of marker associated with the biological and clinical behavior of breast cancer may eventually be useful to predict a tumors response to adjuvant chemotherapy (see page 175).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Esteva to measure levels of HER-3 prior to treating a patient with an anti-EGFR antibody because Esteva teaches that HER-3 is known to be associated with insensitivity to chemotherapeutic agents and because HER-3 is known to be activated by ligands for other HER receptors, such as EGF and betacellulin. One would have been motivated by the teachings of Esteva that HER-3 levels are associated with insensitivity to chemotherapeutic agents because anti-EGFR antibodies are often used together with chemotherapeutic agents in the treatment of cancer as taught by Hudziak.

Claims 29-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudziak (US 5,770,195; issued Jun. 23, 1998) in view of Esteva (Esteva, F. J. et al., Pathology Oncology Research, 7(3): 171-177, 2001) and further in view of Yang (Yang, X.-D. et al., Critical Reviews in Oncology/Hematology, 38: 17-23, 2001).

The claimed methods comprise two active steps: that of assaying for the expression level of HER3 in cells from a cancer and the second step of treating the subject with an EGFR antibody if the HER3 expression levels detected have an OD less than 9 when determined by quantitative immunohistochemistry that the subject is treated. The claims encompass the use of antibody that is encompassed by the term "ABX-0303".

Hudziak and Esteva teach as set forth above. Neither Hudziak nor Estava teaches the ABX-0303 antibody or antibodies.

However, ABX-0303 appears to be a useful anti-EGFR antibody, because Yang teaches that it is a completely human antibody, and because it completely eradicates a human tumor xenograft (see page 20, section 2.3). Also, Yang teaches that the antibody appears to be useful in xenografts that express high levels of EGFR. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used Yang's ABX-EGF antibody. One would have been motivated by the teachings of Yang with regard to efficacy of the ABX-EGF antibody and also because the ABX-EGF antibody is a fully human antibody which lessen the immune response that a human subject would have to the administration of an antibody.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
March 26, 2008
/Alana M. Harris, Ph.D./
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